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Research Review: The role of diet in the treatment of attention-deficit/hyperactivity disorder – an appraisal of the evidence on efficacy and recommendations on the design of future studies

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Background: The efficacy of three dietary treatments for ADHD has been repeatedly tested in randomized controlled trials (RCTs). These interventions are restricted elimination diets (RED), artificial food colour elimination (AFCE) and supplementation with free fatty acids (SFFA). There have been three systematic reviews and associated meta-analyses of the RCTs for each of these treatments. **Scope:** The aim of this review is to critically appraise the studies on the dietary treatments of ADHD, to compare the various meta-analyses of their efficacy that have been published and to identify where the design of such RCTs could be improved and where further investigations are needed. **Findings:** The meta-analyses differ in the inclusion and exclusion criteria applied to potentially eligible studies. The range of average effect sizes in standard deviation units is RED (0.29–1.2), AFCE (0.18–0.42) and SFFA (0.17–0.31). The methodology of many of the trials on which the meta-analyses are based is weak. **Conclusions:** Nevertheless, there is evidence from well-conducted studies for a small effect of SFFA. Restricted elimination diets may be beneficial, but large-scale studies are needed on unselected children, using blind assessment and including assessment of long-term outcome. Artificial food colour elimination is a potentially valuable treatment but its effect size remains uncertain, as does the type of child for whom it is likely to be efficacious. There are additional dietary supplements that have been used with children with ADHD. A systematic search identified 11 RCTs that investigated the effects of these food supplements. Despite positive results for some individual trials, more studies are required before conclusions can be reached on the value in reducing ADHD symptoms of any of these additional supplements. **Keywords:** ADHD, meta-analysis, food colours, fatty acid, elimination diet, food supplements.

Introduction

Attention deficit/hyperactivity disorder (ADHD) or its more severe counterpart hyperkinetic disorder (Lee et al., 2008) is an increasingly prevalent (Gelahun et al., 2013; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) and impairing behavioural disorder that emerges during the early years and can endure through into adulthood (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Its aetiology is complex. Genetic factors play an important role (Elia et al., 2012), but their full effects may only become apparent when their interaction with environment is taken into account. Indeed, environmental factors are important too, e.g., institutional care (Kreppner, O'Connor, & Rutter, 2001) and maternal smoking during pregnancy (Schmitz et al., 2006), as are a wide range of adverse experiential factors that affect the central nervous system (Taylor, 1999), e.g., premature birth (Bhutta, Cleves, Casey, Craddock, & Anand, 2002). Dietary factors have been implicated as well, including artificial food additives (Nigg, Lewis, Edinger, & Falk, 2012; Schab & Trinh, 2004), food sensitivities (Pelsser, Buitelaar, & Savelkoul, 2009), trace element deficiencies (Hurt, Arnold, & Lofthouse, 2011), including iron (Cortese, Angriman, Lecendreux, & Konofal, 2012), free fatty acid deficiencies (Schuchardt, Huss, Stauss-Grabo, & Hahn, 2010), a 'Western' style of diet (Howard et al., 2011) and food insecurity (i.e. poor nutrition) (Melchior et al., 2012).

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Treatment for ADHD normally begins during the school years and multimodal approaches are recommended and usually include psychostimulant medicines (NICE, 2008; Taylor et al., 2004). A meta-analysis suggested that, after corrections for publication bias, the effect size on ADHD symptoms for methylphenidate and for amphetamine are 0.72 and 0.99, respectively (Faraone & Buitelaar, 2010). Although pharmacological treatments for ADHD have shown these large effects, there are a number of factors potentially limiting the use of pharmacological treatments including common although in general manageable, adverse effects on sleep, appetite and growth and uncertainties about potential long-term adverse effects on the brain and cardiovascular system (Graham et al., 2011). Indeed, one major reason for considering alternatives to pharmacological treatment is that parents may have concerns about the use of medication to manage their child's behaviour (Berger, Dor, Nevo, & Goldzweig, 2008) and some parents (and young people) would also prefer a nonpharmacological intervention if an effective one were available (Cormier & Elder, 2007).

Recently, nonpharmacological interventions for ADHD were appraised in a set of meta-analyses conducted using a common systematic search and a rigorous coding and data extraction strategy across treatment domains (Sonuga-Barke et al., 2013). Electronic databases were searched to identify published RCTs that involved individuals who were diagnosed with ADHD (or who met a validated cut-off on a recognized rating scale) and that included an ADHD outcome. The efficacy was assessed of dietary (restricted elimination diets, artificial food colour exclusions and free fatty acid supplementation) and psychological (cognitive training, neurofeedback and behavioural interventions) ADHD treatments. The measure of effect used was the standardised mean difference (SMD). This assesses how many standard deviation units difference was found between the mean ADHD scores under the treatment and control conditions. This is a widely used measure of effect size that is independent of the scales being used. One method of calculating the SMD is referred to as Cohen's d. When the outcome measure was based on ADHD assessments by raters closest to the therapeutic setting, all dietary (SMD = 0.21–0.48) and all psychological (SMD = 0.40–0.64) treatments produced statistically significant effects. The best probably blinded ratings were either made under blinded conditions (e.g. placebo-controlled trial) or by a significant adult (e.g. a teacher) or an observer unaware of treatment allocation. When the best probably blinded assessment was employed, the above effect remained significant for free fatty acid supplementation (SMD = 0.16) and artificial food colour exclusion (SMD = 0.42) but was substantially attenuated to nonsignificant levels for all other treatments.

The aim of this review is to critically appraise the studies on the dietary treatments of ADHD, to compare the various meta-analyses of their efficacy that have been published and to identify where the design of such RCTs could be improved and where further investigations are needed.

Dietary interventions for ADHD

There are three dietary treatments for ADHD which have been tested in repeated RCTs. (a) Restricted elimination diets (RED): this involves the removal from the diet of food stuffs to which the child shows hypersensitivity by exacerbations of behavioural symptoms of ADHD. This hypersensitivity may either be allergic (i.e. IgE-mediated) or nonallergic. (b) Artificial food colours exclusion (AFCE): this can be applied as recommended as part of the Feingold diet (Feingold, 1975) or in isolation. (c) Supplementation with free fatty acids (SFFA): it has been reported that compared to healthy controls children with ADHD show deficiencies in FFA (Milte, Sinn, & Howe, 2009). FFA have an important role in brain growth and development (Raz & Gabis, 2009). Increasing the amount of FFA in the diet would be expected to counter any FFA deficit and thereby possibly improve brain functioning and behaviour (Johnson et al., 2012).

In RED, the interventions usually involved the testing of an individually constructed restricted elimination diet (sometimes referred to as an oligoantigenic diet), which consists of some hypoallergenic foods. This is often followed by food challenges to test whether specific foods might trigger ADHD behaviours, i.e., to identify a hypersensitivity behavioural reaction to foods. The RED studies vary in how strictly the elimination of these specific foods is applied.

For AFCE, interventions involve the testing of the effects of removing food colours from the child's diet. These colours were often azo dyes and included tartrazine, carmoisine, sunset yellow, brilliant blue, indigotine, allura red, quinoline yellow and ponceau 4R. Sometimes, the removal of colours was part of a broader elimination diet such as the Feingold diet or Kaiser Permanente diet. The intervention usually investigated the effect over periods of a week or longer. Some studies examined the acute immediate effects of food challenges that included colours.

The SFFA interventions comprise supplementation of the diet with free fatty acids (FFA) or related compounds. The omega-3 free fatty acids included α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) and the omega-6 free fatty acids included γ-linolenic acid (GLA), linoleic acid (LA) and arachidonic acid (AA). This supplementation is usually achieved by administering a capsule-containing oils or in a few studies by introducing diets rich in fish products. The effects are usually tested of supplementation for periods of a week or longer.

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There have been a number of RCTs of supplements other than FFA. We conducted a search up to 3 April 2012 which identified 2,785 unique records of which 2,723 were screened out on the basis of the title and abstract. On the remaining 63, 20 were not about ADHD or did not have an ADHD-related outcome, 12 were not RCTs, 14 were not 'other supplements' as defined in the protocol, including two trials of personalized homoeopathy (Frei, Everts, & von Ammon, 2005; Jacobs, Williams, Girard, Njike, & Katz, 2005) and one trial of liothyronine (L-T-3) on children with ADHD and resistance to thyroid hormone (Weiss, Stein, & Refetoff, 1997), four in which supplements were adjuncts to other treatments, and one which included patients who were too old. Thus 11 trials were identified that investigated the effects of food supplements other than FFA that met the inclusion criteria. These covered a wide range of substances from minerals (zinc – Arnold et al., 2011; Bilici et al., 2004 and iron – Konofal et al., 2008), vitamins (Haslam, Dalby, & Rademaker, 1984), natural stimulants (caffeine – Garfinkel, Webster, & Loman, 1981 and St John's Wort – Weber et al., 2011), bark extracts (Trebaticka et al., 2006), amino acids (tyrosine, tryptophan both in one trial – Nemzer, Arnold, Votolato, & McConnell, 1986), carnitine (Arnold et al., 2007; Van Oudheusden & Scholte, 2002) and aspartame (Shaywitz et al., 1994). Only eight of these trials reported sufficient data to calculate SMD between active and control conditions using the approaches allowed in the protocol.

Despite positive results for some individual trials, there was no consistent finding of significant reductions in ADHD symptoms for any one supplement. For instance, significant effects were seen in one of the two qualifying trials for zinc (SMD = 1.06) (Bilici et al., 2004) and carnitine (SMD = 1.38 (parent rating), 0.86 (teacher rating) based on the number of responders on carnitine compared with placebo) (Van Oudheusden & Scholte, 2002). However, in each case, the second more recent trial for zinc (Arnold et al., 2011; SMD = 0.02) and for carnitine (Arnold et al., 2007; SMD = 0.23) did not show a significant effect. Early reports of initial evidence for small beneficial effects on ADHD of low doses of caffeine (Garfinkel et al., 1981), but this was a trial with a very small number of participants, nonlinear effects of caffeine dose and interactions with methylphenidate. For tryptophan, there were significant effects on parent (SMD = 0.99) but not teacher ratings (SMD = 0.03) (Nemzer et al., 1986) and a significant effect of supplementation with St John's Wort extract (Weber et al., 2011; SMD = 0.56). These interventions require further trials before any firm conclusions can be reached about their possible efficacy in treating ADHD. For other inventions, there is as yet no indication of possible benefits. Individual trials of iron (Konofal et al., 2008), vitamins (Haslam et al., 1984), bark extracts (Trebaticka et al., 2006), tyrosine (Nemzer et al., 1986) and aspartame (Shaywitz et al., 1994) were all negative on the main outcome measures.

These studies on other supplements have mainly centred on singled nutrient treatments. There are broad-spectrum micronutrient treatments but to date the positive findings for these treatments applied to ADHD are sparse and RCTs need to be conducted (Rucklidge & Kaplan, 2013). Having considered the wider range of dietary treatments for ADHD, we will now return to the three treatments where replicated RCTs are available and compare the various meta-analyses that have been published on their efficacy.

Meta-analyses on restricted elimination diets. A meta-analysis by Pelsser (2011) obtained an effect size for RED of 1.2 for children with ADHD. A second meta-analysis by Nigg et al. (2012) reported a much smaller pooled effect size of 0.29. This lower figure resulted from the exclusion of two studies with a large but outlier effect size (Pelsser et al., 2011; Pelsser, Frankena et al., 2009). A third meta-analysis (Sonuga-Barke et al., 2013) reported an effect size of 1.48 but when the analysis was restricted to studies with assessments made by raters who were probably blind as to treatment, the effect size fell to 0.51 and just failed to reach significance. This analysis of blind ratings only excluded the two outlier studies also excluded by Nigg et al. (2012).

Figure 1 provides a summary of the effect sizes reported in these meta-analyses based upon ratings of behaviour. In the case of Sonuga-Barke et al. (2013), only the results based on probably blind ratings are included. The effect sizes in Figure 1 from Nigg et al. (2012) (SMD = 0.29) and Sonuga-Barke et al. (2013) (SMD = 0.51) both exclude the Pelsser studies. These two meta-analyses provide an average SMD of 0.40 for RED.

Meta-analyses on artificial food colour elimination. Effect sizes of 0.21 and 0.22 for high-quality studies on AFCE have been reported by Schab and Trinh (2004) and by Nigg et al. (2012). However, these meta-analyses of AFCE were not restricted to

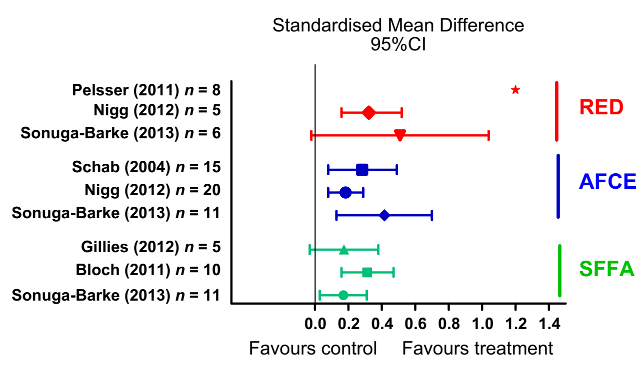

Figure 1 Summary of meta-analysis effect sizes for dietary treatments of ADHD (*n*: number of included studies)

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children with an ADHD diagnosis. A somewhat higher effects size for AFCE (SMD = 0.42) for children with ADHD has been reported (Sonuga-Barke et al., 2013) (see Figure 1) based on probably blinded ratings. The average SMD for the studies that were included in both the Sonuga-Barke et al. (2013) and Nigg et al. (2012) analyses were very similar (0.35 and 0.37, respectively).

Meta-analyses on supplementation with free fatty acids. Five systematic reviews on SFFA have been published (Bloch & Qawasmi, 2011; Gillies, Sinn, Lad, Leach, & Ross, 2012; Ramakrishnan, Imhoff-Kunsch, & DiGirolamo, 2009; Raz & Gabis, 2009; Transler, Eilander, Mitchell, & van der Meer, 2010) including two meta-analyses (Bloch & Qawasmi, 2011; Gillies et al., 2012). The review by Bloch and Qawasmi (2011) was quantitative but limited to studies on omega-3 supplementation i.e. excluded studies on omega-6. It also was not limited to studies on children with ADHD. An overall SMD of 0.31 was reported. The efficacy of SFFA as a treatment for ADHD showed a somewhat weaker effect in Sonuga-Barke et al. (2013). The modest SMD of 0.21 falls, though remains significant, when the analysis is applied ratings that were probably blind (SMD = 0.17).

The meta-analysis by Gillies et al. (2012) suggested a similar effect size for parent report of ADHD symptoms (SMD = 0.17). In this case, the effect was not significant as the number of trials included were fewer than reported by Sonuga-Barke et al. (2013). The latter was able to include Hirayama, Hamazaki, and Terasawa (2004) having obtained means and standard deviations from the author. Two further papers were included by imputing standard deviations (Aman, Mitchell, & Turbott, 1987) and by the use of pretest standard deviations (Belanger et al., 2009).

One feature of the SFFA studies is the wide range of combinations of fatty acids being tested and this makes it problematic to produce a quantitative estimate the benefits to be obtain from specific combinations and dosages of fatty acids. However, it has been observed that possibly a combination of EPA, DHA and GLA is most likely to be efficacious (Hurt et al., 2011; Schuchardt et al., 2010).

Since these meta-analyses have been published, one additional RCT has been published on the effects of SFFA on the behaviour of children with ADHD (Milte et al., 2012). Using an outcome measure of the parent-rated ADHD index, this study provides an effect size of 0.23 derived from the estimate and its standard error for eicosapentaenoic acid versus linoleic acid (control) at the 4-month outcome.

For the SFFA studies in Sonuga-Barke et al. (2013), it has been possible to examine whether there is an effect of treatment on specific aspects of AHDH, i.e., inattention and impulsivity/overactivity. In neither case, the effect was significant (SMD = 0.11 and 0.13, respectively). Similarly, there was no evidence for a beneficial effect of SFFA on symptoms of oppositional defiant disorder or conduct disorder (SMD = 0.09). These analyses were not possible for the AFCE and RED treatments in Sonuga-Barke et al. (2013) as these outcome measures were not reported.

Comparing meta-analyses of dietary treatments

The comparison between the various meta-analyses that have been published on dietary treatments for ADHD-related behaviours has shown that no one meta-analysis can be considered definitive. The meta-analyses differ in the inclusion criteria for studies based on the participant characteristics and the form of treatment applied. Choices are made on which outcome measure to adopt and in the way calculations of effects size are conducted, e.g., whether to use pooled pretest *SD*s for pre-/post-test designs, and on the use of imputed *SD* values. There are differences in the way outliers are dealt with (Viechtbauer & Cheung, 2010) and in whether or not to correct for publication bias. These differences will inevitably result in different values for the aggregated effect size. However, there are some aspects of meta-analysis methodology where specific options should employed. The RCTs whose effects are being aggregated are based on different samples, by different investigators and using different designs. Consequently, fixed effect models are not appropriate and random effects model should be employed. Judgements about the value of particular treatments needs to be made based on the pattern of results produced by the published meta-analyses and not on one alone.

Methodological considerations for future RCTs on dietary treatments for ADHD

Blind assessment of outcome. The RED trials in Sonuga-Barke et al. (2013) are a mix of cross-over and parallel group RCTs. Three studies tested RED by food challenges while on RED (Boris & Mandel, 1994; Carter et al., 1993; Egger, Carter, Graham, Gumley, & Soothill, 1985) and four studies tested for the effects of RED against control diets (Kaplan, McNicol, Conte, & Moghadam, 1989; Pelsser, Buitelaar et al., 2009; Pelsser, Frankena et al., 2009 Pelsser et al., 2011; Schmidt et al., 1997). The RED results suggest high heterogeneity and need to be treated with caution. This heterogeneity can arise from a number of sources including variation in how strictly food elimination is applied. It is also influenced by two extreme SMDs (Pelsser, Buitelaar et al., 2009; Pelsser et al., 2011; Pelsser, Frankena et al., 2009) where there are concerns over the blinding of assessments (Adesman, 2011; Barkley, 2012). In the first open label phase of Pelsser et al. (2011), the blinded assessments were performed by a masked paediatrician but was in part

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based on information on behaviour provided by parents who were *not* blind as to treatment. The parents and teachers were aware of whether the children received the elimination diet or not in this phase of the study. This means that there are no assessments of outcome based on information about the children's behaviour provided by reporters blind as to treatment condition. The second double-blind phase of the study was focused only on the clinical responders and was designed just to examine whether IgG content of food predicted clinical response (which appeared not to be the case). Pelsser, Buitelaar et al., (2009) and Pelsser, Frankena et al., (2009) was a nonblinded open-label trial of RED. The outcome measures were based on parent and teacher reports. These could not be blinded as they had to supervise the food intake of the child and knew whether the child was following an elimination diet. The absence of blind ratings makes it difficult to judge the value of RED from these Pelsser studies.

Reliance on rating scales. Quantitative approaches to the measurement of ADHD-related functions have been shown to be sensitive to change under treatment (Wehmeier et al., 2012). Attention measures such as those derived from the CPT (Huang-Pollock, Karalunas, Tam, & Moore, 2012), measures of executive function (Lambek et al., 2011) and response inhibition (e.g. stop signal tasks) (Raiker, Rapport, Kofler, & Sarver, 2012) have all been investigated as candidates for neuropsychological markers of ADHD. These approaches to the assessment of outcome in treatment trials are valuable as they facilitate obtaining blinded measures. There is however as yet no widely adopted set of neuropsychological markers being used as indicators of improvement under treatment.

As a consequence, reliance must still be placed on reports from teacher, parents and others on the child's behaviour. In many ways, parents are in an ideal position to monitor behaviour changes in their child. However, for a number of the dietary treatments, especially those based on an exclusion diet, it is problematic for parents to be masked from the treatment being used. It is therefore desirable to use observers of the children who can maintain such blindness. Such masked ratings could be obtained from teachers. If this is not possible, then a more costly option is to use independent observers in the classroom setting (Abikoff et al., 2002). These have been used to monitor behaviour change under dietary modifications (McCann et al., 2007).

A feature of the dietary treatment studies is the use of multiple scales and multiple informants. This leaves the studies open to outcome selection bias unless there is pre-trial registration of the study that includes the specification primary outcomes (Chan & Altman, 2005). Trial registration has other benefits too, for example, in reducing publication bias. However, despite a marked increase in the number of clinical trials on children being registered, there is still a substantial number of studies failing to make results available (Shamliyan & Kane, 2012). It is important too for meta-analyses to be registered and for their protocols to include a specification of the outcomes measures to be analysed.

The continuing concerns about obtaining behaviour ratings truly blind to treatment, means that trials need to be designed in ways that incorporate a range of methods of assessing outcome. Obtaining converging evidence of efficacy from rating scales, objective laboratory tests and from the recording of behaviour by independent observers should provide optimal appraisal of treatment efficacy.

Participant selection. There is an element of selection for sensitivity to certain foods before entry to the RCT in some studies of RED (Boris & Mandel, 1994; Carter et al., 1993; Egger et al., 1985), which will limit the generalizability of the results to all children with ADHD. In Sonuga-Barke et al. (2013), there were only two studies that were free of these concerns over blinding and over selectivity (Kaplan et al., 1989; Schmidt et al., 1997). The weighted average SMD for these two studies for probably blinded ratings is 0.12. This effect size suggests that for ADHD children in general RED may have little benefit but that for those with suspected food sensitivities RED may have a value in treatment. It should be noted that the exclusions and challenges in the RED studies also included food colour.

The same question of selectivity in the ADHD participants arises with the AFCE studies and this may limit the generalizability of the results. In Sonuga-Barke et al. (2013), there were 3 AFCE studies where the RCT was applied to children not already suspected to be responders to food colours (Conners, Goyette, Southwick, Lees, & Andrulonis, 1976; Harley et al., 1978; Williams, Cram, Tausig, & Webster, 1978). These studies produced a weighted average SMD = 0.24. This suggests that the value of AFCE may be greatest for those already suspected of being sensitive to food colours but that a broader group of children with ADHD may also benefit.

In line with this conclusion, the results of studies on children from the general population have shown that food colours can have an impact on ADHD behaviour across the range of initial symptom severity (Bateman et al., 2004; McCann et al., 2007) with effect sizes of around 0.18. This is somewhat lower than found for children with ADHD in the Sonuga-Barke et al. (2013) meta-analysis but in line with the results from the wider ranging meta-analyses by Schab and Trinh (2004) (SMD = 0.21 for better quality studies), Nigg et al. (2012) (SMD = 0.22 based high-quality studies confined to colour additives) and for the studies on samples not selected for prior sensitivity in the Sonuga-Barke et al. (2013) meta-analysis (SMD = 0.24, see above).

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There is no good reason from the studies of SFFA to suppose that there is greater benefit for those with initially low levels of fatty acids in the blood (Johnson et al., 2012; Milte et al., 2012). The issue of which children might benefit most from SFFA remains an open question though it has been suggested that children with ADHD and comorbid learning difficulties may show the greatest benefit (Milte et al., 2012).

Methods of data analysis. A salient feature of the AFCE studies on children with ADHD is that these were undertaken over 30 years ago. For AFCE, there were no studies published after 1981 that met the inclusion criteria for the Sonuga-Barke et al. (2013) systematic review and meta-analysis. The AFCE studies were a mix of cross-over trials of food challenges whilst on an additive free diet and two studies of elimination and control diets (Conners et al., 1976; Williams et al., 1978). As these studies were undertaken, more powerful methods of data analysis have become available. This is particularly the case for cross-over studies where mixed linear modelling can be applied (Gueorguieva & Krystal, 2004). There are additional possibilities for modelling inter-subject variability in treatment response by applying such methods to cross-over designs (Senn, Rolfe, & Julious, 2011). Given the marked differences in ADHD children's response to dietary treatments exploring this issue in larger samples of children with ADHD to determine which children may be best suited to which treatment is an essential next step.

Associated conditions. The SMDs obtained for SFFA in the Sonuga-Barke et al. (2013) analysis are somewhat lower than reported by Bloch and Qawasmi (2011) (SMD = 0.31). This may be due to less strict inclusion criteria on evidence of ADHD diagnosis being applied by Bloch and Qawasmi (2011) who included studies on children with specific learning disabilities (Richardson & Puri, 2002), developmental coordination disorders (Richardson & Montgomery, 2005) and impaired sustained visual attention (Vaisman et al., 2008) and was not limited to children with ADHD. It may therefore be that SFFA has a larger impact on ADHD behaviours in children with other conditions often associated with ADHD, than on children with ADHD itself.

Choice of placebo. The trials on SFFA are a mix of cross-over or parallel group RCTs. In general, the blinding was good, but there are possible reservations over the use of vitamin C as placebo control in one study (Raz, Carasso, & Yehuda, 2009). However, there may be problems with blinding as the placebo and active treatments may differ in side-effects such a 'fishy-after taste'. SFFA studies should test whether blinding has been maintained and adopt procedures to preserve blindness (Sontrop & Campbell, 2006).

It is possible that some of the other control/placebo substances may be active. For example, sunflower oil was used as the placebo in a test of the effect of omega-3 fatty acid (Belanger et al., 2009). Sunflower oil contains omega-6 fatty acid and in other studies might be considered an active treatment. Such a beneficial effect of the placebo would be a conservative feature of the design and would act against detecting an effect of SFFA. Nevertheless with possibly only small effect sizes, studies need to protect against such Type II errors.

Statistical power. There are insufficient repeated trials of the effects of specific supplements to make an assessment of the efficacy of Other Supplements. Clearly, if there are a priori reasons to believe that some of these supplements may be beneficial it is important that more RCTs are conducted and with adequate power to detect possible changes to ADHD behaviours. Specifically power calculations need to be based on realistic anticipated effects. The more extensively studied treatments, such as AFCE and SFFA, are finding only small effect sizes (around 0.20). Studies on all dietary treatments need to be designed with putative effect sizes no greater than this. To have 80% power to detect such an effect size at $p < .05$ (one-sided), two samples of 310 are required.

Non-ADHD behaviours as outcomes. In investigating the effects of dietary treatments on children with ADHD, the studies reviewed almost exclusively monitored outcome in terms of ADHD behaviours. In Sonuga-Barke et al. (2013), none of the RED or AFCE studies provided probably blinded measures on oppositional defiant disorder and conduct disorder behaviours. For SFFA, 9 studies did employ a wider range of outcomes. Given the finding of a larger SMD for SFFA with children with a variety of associated conditions (Bloch & Qawasmi, 2011), it would be appropriate for future studies to incorporate measures of other behaviours as secondary outcomes in dietary trials.

Long-term outcome. The RCTs of treatment efficacy in Sonuga-Barke et al. (2013) monitored behaviour over relatively short periods of time. The longest duration of treatment for RED was 5 weeks (Pelsser, Buitelaar et al., 2009; Pelsser et al., 2011; Pelsser, Frankena et al., 2009). For the AFCE studies, 8 week was the maximum period of treatment (Adams, 1981), and for SFFA, it was 4 months (Milte et al., 2012; Stevens et al., 2003; Voigt et al., 2001). The dietary treatment of ADHD is only likely to be effective if it sustained over a long period of time. If the diet changes are terminated, it is probable that the ADHD behaviour will returned to the former level of severity. For this reason, it is important to establish the course of behaviour changes in response to treatment over the medium and long term.

Safety of diet treatments. When diets are changed, the implications for physical health need to be

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considered. In Sonuga-Barke et al. (2013), 9 of the 12 RCTs on SFFA made comments on either health safety or adverse events and 6 studies made a formal appraisal of adverse events during the trial. In none of the 12 trials, adverse events were significantly associated with the SFFA treatment. The symptoms noted were minor episodes of symptoms such as dyspepsia (Manor et al., 2012), diarrhoea (Gustafsson et al., 2010) and occasional nose bleeds (Milte et al., 2012).

By contrast, the studies on AFCE and RED did not formally report on adverse effects, with the exception of Pelsser et al. (2011) where no incidents were found. However the AFCE and RED studies were often conducted in the context of on-going monitoring of food intolerances and the childrens' health was under review by clinicians. It seems unlikely that the exclusion of artificial food colours would have an adverse effect on health via any nutritional deficiency as foods with alternative natural colours are readily available. RED is more of a concern. There is a need to monitor children nutritional status, growth and general health whilst undergoing the dietary exclusions in RED (NICE, 2008). This requires a multidisciplinary team approach to treatment, and this may limit the availability of this treatment approach.

As well as concerns about possible adverse effects of physical health, the possible impact on other aspects of the child's mental health needs to be considered. The only study to report on the children's reaction having to make dietary changes was that provided by Pelsser et al. (2011) and these anecdotal reports were positive. Future studies should continue to monitor possible adverse effects on the child's well-being of not being allowed to have the food their friends have.

Mediating biological mechanisms. The evidence for possible biomarkers for ADHD has been systematically reviewed by Scassellati, Bonvicini, Faraone, and Gennarelli (2012). They define a biomarker as 'a characteristic that can be objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process, or a response to a therapeutic intervention'. The Scassellati et al. (2012) meta-analyses suggested a number of possible candidates for biomarkers for ADHD based on case/control comparisons: norepinephrine, 3-Methoxy-4-hydroxyphenylethylene glycol, monoamine oxidase, zinc and cortisol. Such studies comparing cases and controls are unable to clearly establish cause and effect in relation to ADHD symptomatology. However, evidence from changes in putative biomarkers in response to treatment provides available additional evidence of a possible causal relationship between the biomarker and ADHD. Dietary treatment studies should consider whether it is feasible to incorporate the measurement of change in these general ADHD markers.

These biomarkers, however, may be somewhat remote from the action of dietary treatments with many intervening physiological processes. For each of the three main dietary treatments being considered here, there are plausible biological mechanisms mediating their effects. However, to date, there are few studies monitoring changes in mediators. Even for SFFA, where this has been most extensively studied, the results are unclear. For example, a relationship was found between the ratio of omega-6/omega-3 fatty acid levels and the response to SFFA (Gustafsson et al., 2010). Johnson, Ostlund, Fransson, Kadesjö, and Gillberg (2009) too found such an association but used a different definition of responder (reduction in ADHD behaviours rather than high ODD symptoms at baseline). Using a correlational approach, Milte et al. (2012) did not find significant associations between changes in FFA levels and ADHD behaviour in the sample as a whole, but did find such associations for children with learning difficulties. These associations between changes in the omega-6/omega-3 ratio levels are suggestive of possible biological mechanisms but have only been investigated in plasma and red blood cell phospholipids, as yet the significance of such change for brain cell membranes has not been established.

There is other evidence suggesting a possible biological basis for the benefits of SFFA for children with ADHD. One study has found that polymorphisms in genes involved in fatty acid metabolism are associated with ADHD (Brookes, Chen, Xu, Taylor, & Asherson, 2006). Abnormalities in emotion-elicited event-related potentials have been shown to be related to lower omega-3 fatty acid levels in children with ADHD (Gow et al., 2013).

The main focus in studies on RED has been on whether the effects are mediated by an allergic mechanism. The most extensive test of this possibility found no evidence that the mechanisms of food sensitivity were IgE mediated nor were they related to IgG levels in children (Pelsser et al., 2011). This suggests that food sensitivities being addressed by RED are not mediated by allergic mechanisms (Pelsser, Buitelaar et al., 2009; Pelsser, Frankena et al., 2009). There is a range of immunological and genetic mechanisms that might underlie the food hypersensitivity shown by some children with ADHD. Pelsser, Buitelaar et al. (2009) and Pelsser, Frankena et al. (2009) have identified a number of suggested biomarkers that might be incorporated to monitor concomitant change under dietary treatment.

Similarly, it has been suggested that the effects of AFCE are not mediated by allergic mechanisms but by a nonspecific pharmacological effect that would be similar in children irrespective of their atopic status and that was mediated by histamine release (Pollock & Warner, 1990). Indirect evidence in support of such a mechanism was the identification of polymorphisms in the histamine N-methyltransferase gene as being moderators of the impact of food additives, including colours, on hyperactivity in

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children (Stevenson et al., 2010). As with RED and SFFA, the proposed mechanisms for the influence ACFE on behaviour in children with ADHD are poorly understood. There would be considerable benefits from future RCTs including biological measures designed to elucidate these mechanisms.

There is a need to use studies informed by possible mechanisms to address the question of why some children respond to particular dietary treatments and other do not. These persons by treatment interactions make demands on sample size for adequate power. One prime motivation for such studies is that they will inform clinical decisions attempting to identify optimal treatment for particular children. Increasingly, genetic differences between children are being examined as possible origins of such person by treatment interactions. The study mentioned above by Stevenson et al. (2010) is one example of genetic polymorphisms that appear to moderate the impact of diet on ADHD behaviours. Such genotyping can now be carried out with little cost and could be readily obtained in dietary treatment studies. Even though there may be reluctance to use such genetic information to guide treatment decisions, the findings from such genetically informed studies can shed light on biological mediating mechanisms. Overviews of the methods for testing RCTs for mediation can be found in Kraemer, Wilson, Fairburn, and Agras (2002), for moderation in Rothwell (2005) and for their combined effects in Rothman (2013).

Conclusions

For SFFA, there is evidence for an effect on ADHD symptoms in children with ADHD. However, it must be recognized that although there will be some variation between children in the response to FFSA supplementation, on average its influence on behaviour in these children is small. The average effect size for the three meta-analyses in Figure 1 is 0.22.

Restricted elimination diets may be beneficial for children with ADHD with a history of adverse reactions to food. All the studies included by Sonuga-Barke et al. (2013) have positive SMDs. The methodological concerns with a number of the studies mean that it is difficult to have confidence in an estimate of the overall effect. The RED meta-analysis effects sizes summarized in Figure 1 include one by Pelsser which incorporate results from the Pelsser studies which, for the reasons related to blinding discussed above, need to be excluded. On the basis of the Nigg et al. (2012) and Sonuga-Barke et al. (2013) results, an average SMD effects size for RED is around 0.40. Before this approach to treatment can be unequivocally recommended for children with ADHD in general, it is essential that large-scale studies are undertaken that have three key design features. First, it is based on a sample of children with ADHD who have not been selected on the basis of previous responses to food stuffs. Second, the study includes observations of the children's' behaviour by a reporter who is truly blind as to dietary treatment. Third, to control for nonspecific treatment effects, head-to-head studies of RED and treatment alternatives including control diets and/or treatment-as-usual need to be conducted (Rommelse & Buitelaar, 2013).

Artificial food colours exclusion may be beneficial for children thought to be adverse responders to food colour exposure. However, for AFCE to be recommended for children with ADHD in general, there is an urgent need for a study using more refined methodologies and incorporating blind assessments applied to unselected samples of children with ADHD, i.e., not those already suspected of being responders. The results suggest that food colour elimination is a potentially valuable treatment approach for ADHD. The effect sizes seen for summarised in Figure 1 suggest an average SMD effect size of around 0.30. The figure may be somewhat lower (around 0.22) if estimates are based on studies with high quality outcome measures and adequate blinding as judged by Schab and Trinh (2004) and Nigg et al. (2012). However, without more definitive contemporary studies, the magnitude of the effect of food colour elimination as a treatment for ADHD remains uncertain, as is the range of children with ADHD for whom it is likely to be efficacious. For RED, and particularly AFCE, there is a concern that the studies were undertaken some time ago. It is not clear whether findings will still hold when diets and available food stuffs have changed so markedly in the intervening time period. For example, the use of AFCE has been drastically reduced in the UK in response to a voluntary ban requested by the Food Standards Agency in 2007 (http://food.gov.uk/policy-advice/additivesbranch/foodcolours/colourfree/#.Uoi-FxrxqjW).

For other food supplements, at present, there are too few robust evaluations of their value to inform clinical practice. Larger-scale placebo-controlled RCTs are required.

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Key points

- Supplementation with free fatty acids can have a small beneficial effect on behavior in children with ADHD.
- Restricted elimination diets and artificial food colour elimination may have beneficial effects but there is uncertainty over the size of the effect and the type of child with ADHD likely to benefit.
- The efficacy of a wider range of dietary supplements on the behaviour of children with ADHD has yet to be established.
- There is a need for better designed RCTs on larger samples of children with ADHD to adequately examine the potential value of these dietary approaches to treatment.

References

Abikoff, H.B., Jensen, P., Arnold, L.L.E., Hoza, B., Hechtman, L., Pollack, S., … & Wigal, T. (2002). Observed classroom behavior of children with ADHD: Relationship to gender and comorbidity. *Journal of Abnormal Child Psychology*, *30*, 349–359.

Adams, W. (1981). Lack of behavioral effects from Feingold diet violations. *Perceptual and Motor Skills*, *52*, 307–313.

Adesman, A. (2011). Restricted elimination diet for ADHD. *The Lancet*, *377*, 1567.

Aman, M.G., Mitchell, E.A., & Turbott, S.H. (1987). The effects of essential fatty acid supplementation by Efamol in hyperactive children. *Journal of Abnormal Child Psychology*, *15*, 75–90.

Arnold, L.E., Amato, A., Bozzolo, H., Hollway, J., Cook, A., Ramadan, Y., … & Manos, M. (2007). Acetyl-L-carnitine (ALC) in attention-deficit/hyperactivity disorder: A multi-site, placebo-controlled pilot trial. *Journal of Child and Adolescent Psychopharmacology*, *17*, 791–801.

Arnold, L.E., DiSilvestro, R.A., Bozzolo, D., Bozzolo, H., Crowl, L., Fernandez, S., … & Joseph, E. (2011). Zinc for attention-deficit/hyperactivity disorder: Placebo-controlled double-blind pilot trial alone and combined with amphetamine. *Journal of Child and Adolescent Psychopharmacology*, *21*, 1–19.

Barkley, R.A. (2012). Effectiveness of restricted elimination diets for management of ADHD: Concerns about the INCA study. *The ADHD Report*, *20*, 1–5.

Bateman, B., Warner, J.O., Hutchinson, E., Dean, T., Rowlandson, P., Gant, C., … & Stevenson, J. (2004). The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Archives of Disease in Childhood*, *89*, 506–511.

Belanger, S., Vanasse, M., Spahis, S., Sylvestre, M.P., Lippé, S., L'heureux, F., … & Levy, E. (2009). Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study. *Paediatrics and Child Health*, *14*, 89–98.

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Berger, I., Dor, T., Nevo, Y., & Goldzweig, G. (2008). Attitudes toward Attention-Deficit Hyperactivity Disorder (ADHD) treatment: Parents' and children's perspectives. *Journal of Child Neurology*, *23*, 1036–1042.

Bhutta, A.T., Cleves, M.A., Casey, P.H., Craddock, M.M., & Anand, K.J.S. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm - A meta-analysis. *JAMA*, *288*, 728–737.

Bilici, M., Yildirim, F., Kandil, S., Bekaroğlua, M., Yıldırmışc, S., Değerc, O., … & Aksub, H. (2004). Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Progress Neuro-psychopharmacology and Biological Psychiatry*, *28*, 181–190.

Bloch, M.H., & Qawasmi, A. (2011). Omega-3 fatty acid supplementation for the treatment if children with attention-deficit/hyperactivity disorder symptomatology: Systematic review and meta-analysis. *Journal of the American Academy of Child Adolescent Psychiatry*, *50*, 991–1000.

Boris, M., & Mandel, F.S. (1994). Foods and additives are common causes of the attention deficit hyperactive disorder in children. *Annals of Allergy*, *72*, 462–468.

Brookes, K.J., Chen, W., Xu, X., Taylor, E., & Asherson, P. (2006). Association of fatty acid desaturase genes with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *60*, 1053–1106.

Carter, C.M., Urbanowicz, M., Hemsley, R., Mantilla, L., Strobel, S., Graham, P.J., & Taylor, E. (1993). Effects of a few food diet in attention deficit disorder. *Archives of Disease in Childhood*, *69*, 564–568.

Chan, A.W., & Altman, D.G. (2005). Identifying outcome reporting bias in randomised trials on PubMed: Review of publications and survey of authors. *British Medical Journal*, *330*, 753–756.

Conners, C.K., Goyette, C.H., Southwick, D.A., Lees, J.M., & Andrulonis, P.A. (1976). Food additives and hyperkinesis: A controlled double-blind experiment. *Pediatrics*, *58*, 154–166.

Cormier, E., & Elder, J.H. (2007). Diet and child behavior problems: Fact or fiction? *Pediatric Nursing*, *33*, 138–143.

Cortese, S., Angriman, M., Lecendreux, M., & Konofal, E. (2012). Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. *Expert Reviews of Neurotherapeutics*, *12*, 1227–1240.

Egger, J., Carter, C.M., Graham, P.J., Gumley, D., & Soothill, J.F. (1985). Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. *The Lancet*, *1*, 540–545.

Elia, J., Sackett, J., Turner, T., Schardt, M., Tang, S.C., Kurtz, N., … & Borgmann-Winter, K. (2012). Attention deficit/hyperactivity disorder genomics: Update for clinicians. *Current Psychiatry Reports*, *14*, 579–589.

Faraone, S.V., & Buitelaar, J. (2010). Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *European Child and Adolescent Psychiatry*, *19*, 353–364.

Feingold, B.F. (1975). Hyperkinesis and learning disabilities linked to artificial food flavors and colors. *American Journal of Nursing*, *75*, 797–803.

Frei, H., Everts, R., & von Ammon, K. (2005). Homeopathic treatment of children with attention deficit hyperactivity disorder: A randomised, double blind, placebo controlled crossover trial. *European Journal of Pediatrics*, *164*, 758–767.

Garfinkel, B.D., Webster, C.D., & Loman , L. (1981). Responses to methylphenidate and varied doses of caffeine in children with attention deficit disorder. *Canadian Journal of Psychiatry*, *26*, 395–401.

Gelahun, D., Jacobsen, S.J., Fassett, M.J., Chen, W., Demissie, K., & Rhoads, G.G. (2013). Recent trends in childhood attention-deficit/hyperactivity disorder. *JAMA Pediatrics*, *167*, 282–288.

Gillies, D., Sinn, J.K.H., Lad, S.S., Leach, M.J., & Ross, M.J. (2012). Polyunsaturated fatty acids (PUFA) for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database Systematic Reviews*, 7, CD007986.

Gow, R.V., Sumich, A., Vallee-Tourangeau, F., Crawford, M.A., Ghebremeskel, K., Bueno, A.A., … & Rubia, K. (2013). Omega-3 fatty acids are related to abnormal emotion processing in adolescent boys with attention deficit hyperactivity disorder. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *88*, 419–429.

Graham, J., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., Dittmann, R.W., … & Taylor, E. (2011). European guidelines on managing adverse effects of medication for ADHD. *European Child and Adolescent Psychiatry*, *20*, 17–37.

Gueorguieva, R., & Krystal, J.H. (2004). Move over ANOVA: Progress in analysing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Archives of General Psychiatry*, *61*, 310–317.

Gustafsson, P.A., Birberg-Thornberg, U., Duchén, K., Landgren, M., Malmberg, K., Pelling, H., … & Karlsson, T. (2010). EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD. *Acta Paediatrica*, *99*, 1540–1549.

Harley, J.P., Ray, R.S., Tomasi, L., Eichman, P.L., Matthews, C.G., Chun, R., … & Traisman, E. (1978). Hyperkinesis and food additives: Testing the Feingold hypothesis. *Pediatrics*, *61*, 818–828.

Haslam, R.H., Dalby, J.T., & Rademaker, A.W. (1984). Effects of megavitamin therapy on children with attention deficit disorders. *Pediatrics*, *74*, 103–111.

Hirayama, S., Hamazaki, T., & Terasawa, K. (2004). Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study. *European Journal of Clinical Nutrition*, *58*, 467–473.

Howard, A.L., Robinson, M., Smith, G.J., Ambrosini, G.L., Piek, J.P., & Oddy, W.H. (2011). ADHD Is associated with a "Western" dietary pattern in adolescents. *Journal of Attention Disorders*, *15*, 403–411.

Huang-Pollock, C.L., Karalunas, S.L., Tam, H., & Moore, A.N. (2012). Evaluating vigilance deficits in ADHD: A meta-analysis of CPT performance. *Journal of Abnormal Psychology*, *121*, 360–371.

Hurt, E.A., Arnold, L.E., & Lofthouse, N. (2011). Dietary and nutritional treatments for attention-deficit/hyperactivity disorder: Current research support and recommendations for practitioners. *Current Psychiatry Reports*, *13*, 323–332.

Jacobs, J., Williams, A.L., Girard, C., Njike, V.Y., & Katz, D. (2005). Homeopathy for attention-deficit/hyperactivity disorder: A pilot randomized-controlled trial. *Journal of Alternative and Complementary Medicine*, *11*, 799–806.

Johnson, M., Mansson, J.-E., Ostlund, S., Fransson, G., Areskoug, B., Hjalmarsson, K., … & Gillberg, C. (2012). Fatty acids in ADHD: Plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. *Attention Deficit Hyperactivity Disorder*, *4*, 199–204.

Johnson, M., Ostlund, S., Fransson, G., Kadesjö, B., & Gillberg, C. (2009). Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: A randomized placebo-controlled trial in children and adolescents. *Journal of Attention Disorders*, *12*, 394–401.

Kaplan, B.J., McNicol, J., Conte, R.A., & Moghadam, H.K. (1989). Dietary replacement in preschool-aged hyperactive boys. *Pediatrics*, *83*, 7–17.

Konofal, E., Lecendreux, M., Deron, J., Marchand, M., Cortese, S., Zaïm, M., … & Arnulf, I. (2008). Effects of iron supplementation on attention deficit hyperactivity disorder in children. *Pediatric Neurology*, *38*, 20–26.

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Kraemer, H.C., Wilson, G.T., Fairburn, C.G., & Agras, W.S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*, *59*, 877–883.

Kreppner, J.M., O'Connor, T.G., & Rutter, M. & Romanian Adoptees Study Team. (2001). Can inattentive/overactivity be an institutional deprivation syndrome? *Journal of Abnormal Child Psychology*, *29*, 513–528.

Lambek, R., Tannock, R., Dalsgaard, S., Trillingsgaard, A., Damm, D., & Thomsen, P.H. (2011). Executive dysfunction in school-age children with ADHD. *Journal of Attention Disorders*, *15*, 646–655.

Lee, S.I., Schachar, R.J., Chen, S.X., Ornstein, T.J., Charach, A., Barr, C., & Ickowicz, A. (2008). Predictive validity of DSM-IV and ICD-10 criteria for ADHD and hyperkinetic disorder. *Journal of Child Psychology and Psychiatry*, *49*, 70–78.

Manor, I., Magen, A., Keidar, D., Rosena, S., Taskera, H., Cohen, T., ... & Weizman, A. (2012). The effects of phostatidylserine containing omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: A double-blind placebo-controlled trial followed by an open-label extension. *European Psychiatry*, *27*, 335–342.

McCann, D., Barrett, A., Cooper, A., Crumpler, D., Dalen, L., Grimshaw, K., ... & Stevenson, J. (2007). Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: A randomised, double-blinded, placebo-controlled trial. *The Lancet*, *370*, 1560–1567.

Melchior, M., Chastang, J.F., Falissard, B., Tremblay, R.E., Cote, S.M., & Boivin, M. (2012). Food insecurity and children's mental health: A prospective birth cohort study. *PloSOne*, *7*, e526615.

Milte, C.M., Parletta, N., Buckley, J.D., Coates, A.M., Young, R.M., & Howe, P.R.C. (2012). Eicosapentaenoic and docosahexaenoic acids, cognition, and behaviour in children with attention-deficit/hyperactivity disorder: A randomized controlled trial. *Nutrition*, *28*, 670–677.

Milte, C.M., Sinn, N., & Howe, P.R.C. (2009). Polyunsaturated fatty acid status in attention deficit hyperactivity disorder, depression, and Alzheimer's disease: Towards an omega-3 index for mental health? *Nutrition Reviews*, *67*, 573–590.

Nemzer, E., Arnold, L.E., Votolato, N.A., & McConnell, H. (1986). Amino acid supplementation as therapy for attention deficit disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *25*, 509–513.

NICE (2008). *Attention Deficit Hyperactivity Disorder: Diagnosis and management of ADHD in children, young people and adults*. NICE clinical guideline 72. London: National Institute for Clinical Excellence.

Nigg, J.T., Lewis, K., Edinger, T., & Falk, M. (2012). Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*, 86–97.

Pelsser, L.M.J. (2011). ADHD, a food-induced hypersensitivity syndrome: in quest of a cause. PhD Thesis. University of Nijmegen.

Pelsser, L.M.J., Buitelaar, J.K., & Savelkoul, H.F.J. (2009). ADHD as a (non) allergic hypersensitivity disorder: A hypothesis. *Pediatric Allergy and Immunology*, *20*, 107–112.

Pelsser, L.M., Frankena, K., Toorman, J., Savelkoul, H.F., Dubois, A.E., Pereira, R.R., ... & Buitelaar, J.K. (2011). Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): A randomised controlled trial. *The Lancet*, *377*, 494–503.

Pelsser, L.M.J., Frankena, K., Toorman, J., Savelkoul, H.F., Pereira, R.R., & Buitelaar, J.K. (2009). A randomised controlled trial into the effects of food on ADHD. *European Child and Adolescent Psychiatry*, *18*, 12–19.

Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., & Rohde, L.A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*, 942–948.

Pollock, I., & Warner, J.O. (1990). Effect of artificial food colours on childhood behaviour. *Archives of Disease in Childhood*, *65*, 74–77.

Raiker, J.S., Rapport, M.D., Kofler, M.J., & Sarver, D.E. (2012). Objectively-measured impulsivity and Attention-Deficit/Hyperactivity Disorder (ADHD): Testing competing predictions from the working memory and behavioral inhibition models of ADHD. *Journal of Abnormal Child Psychology*, *40*, 699–713.

Ramakrishnan, U., Imhoff-Kunsch, B., & DiGirolamo, A.M. (2009). Role of docosahexaenoic acid in maternal and child mental health. *American Journal of Clinical Nutrition*, *89*, 958S–962S.

Raz, R., Carasso, R.L., & Yehuda, S. (2009). The influence of short-chain essential fatty acids on children with attention-deficit/hyperactivity disorder: A double-blind placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology*, *19*, 167–177.

Raz, R., & Gabis, L. (2009). Essential fatty acids and attention-deficit-hyperactivity disorder: A systematic review. *Developmental Medicine and Child Neurology*, *51*, 580–592.

Richardson, A.J., & Montgomery, P. (2005). The Oxford-Durham study: A randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*, *115*, 1360–1366.

Richardson, A.J., & Puri, B.K. (2002). A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, *26*, 233–239.

Rommelse, N., & Buitelaar, J. (2013). Is there a future for restricted elimination diets in ADHD clinical practice? *European Child and Adolescent Psychiatry*, *22*, 199–202.

Rothman, A.J. (2013). Exploring connections between moderators and mediators: Commentary on subgroup analyses in intervention research. *Prevention Science*, *14*, 189–192.

Rothwell, P.M. (2005). Subgroup analysis in randomised controlled trials: Importance, indications, and interpretation. *The Lancet*, *365*, 176–186.

Rucklidge, J.J., & Kaplan, B.J. (2013). Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: A systematic review. *Expert Review of Neurotherapeutics*, *13*, 49–73.

Scassellati, C., Bonvicini, C., Faraone, C.V., & Gennarelli, M. (2012). Biomarkers and attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*, 1003–1019.

Schab, D.W., & Trinh, N.H.T. (2004). Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *Journal of Developmental and Behavioral Pediatrics*, *25*, 423–434.

Schmidt, M.H., Mocks, E., Lay, B., Eisert, H.-G., Fojkar, R., Fritz-Sigmund, D., ... & Musaeus, B. (1997). Does oligoantigenic diet influence hyperactive/conduct-disordered children - A controlled trial. *European Child and Adolescent Psychiatry*, *6*, 88–95.

Schmitz, M., Denardin, D., Sliva, T.L., Pianca, T., Hutz, M.H., Faraone, S., & Rohde, L.A. (2006). Smoking during pregnancy and attention-deficit/hyperactivity disorder,

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predominantly inattentive type: A case-control study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*, 1338–1345.

Schuchardt, J.P., Huss, M., Stauss-Grabo, M., & Hahn, A. (2010). Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *European Journal of Pediatrics*, *169*, 149–164.

Senn, S., Rolfe, K., & Julious, S.A. (2011). Investigating variability in patient response to treatment–a case study from a replicate cross-over study. *Statistical Methods in Medical Research*, *20*, 657–666.

Shamliyan, T., & Kane, R.L. (2012). Clinical research involving children: Registration, completeness, and publication. *Pediatrics*, *129*, e1291–e1300.

Shaywitz, B.A., Sullivan, C.M., Anderson, G.M., Gillespie, S.M., Sullivan, B., & Shaywitz, S.E. (1994). Aspartame, behavior, and cognitive function in children with attention-deficit disorder. *Pediatrics*, *93*, 70–75.

Simon, V., Czobor, P., Bálint, S., Mészáros, A., & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. *British Journal of Psychiatry*, *194*, 204–211.

Sontrop, J., & Campbell, M.K. (2006). Omega-3 polyunsaturated fatty acids and depression: A review of the evidence and a methodological critique. *Preventive Medicine*, *42*, 4–13.

Sonuga-Barke, E.J.S., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., Holtmann, M., … & Wong, I.A.C., Sergeant, J. & European ADHD Guidelines Group (2013). Non-pharmacological interventions for Attention-Deficit/Hyperactivity Disorder: Systematic review and meta-analyses of randomised controlled trials of dietary and psychological treatments. *American Journal of Psychiatry*, *170*, 275–289.

Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstad, N., Mahon, A., … & Burgess, J.R. (2003). EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviours. *Lipids*, *38*, 1007–1021.

Stevenson, J., Sonuga-Barke, E., McCann, D., Grimshaw, K., Parker, K.M., Rose-Zerilli, M.J., … & Warner, J.O. (2010). The role of histamine degradation gene polymorphisms in moderating the effects of food additives on children's ADHD symptoms. *American Journal of Psychiatry*, *167*, 1108–1115.

Taylor, E. (1999). Developmental neuropsychopathology of attention deficit and impulsiveness. *Developmental Psychopathology*, *11*, 607–628.

Taylor, E., Döpfner, M., Sergeant, J., Asherson, P., Banaschewski, T., Buitelaar, J., … & Zuddas, A. (2004). European clinical guidelines for hyperkinetic disorder – first upgrade. *European Child and Adolescent Psychiatry*, *13* (Suppl. 1), i7–i30.

Transler, C., Eilander, A., Mitchell, S., & van der Meer, N. (2010). The impact of polyunsaturated fatty acids in reducing child attention deficit and hyperactivity disorders. *Journal of Attention Disorders*, *14*, 232–246.

Trebatická, J., Kopasová, S., Hradečná, Z., Činovský, K., Škodáček, I., Šuba, J., … & Ďuračková, Z. (2006). Treatment of ADHD with French maritime pine bark extract, Pycnogenol. *European Child and Adolescent Psychiatry*, *15*, 329–335.

Vaisman, N., Kaysar, N., Zaruk-Adasha, Y., Pelled, D., Brichon, G., Zwingelstein, G., & Bodennec, J. (2008). Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: Effect of dietary n-3 fatty acids containing phospholipids. *American Journal of Clinical Nutrition*, *87*, 1170–1180.

Van Oudheusden, L., & Scholte, H. (2002). Efficacy of carnitine in the treatment of children with attention-deficit hyperactivity disorder. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *67*, 33–38.

Viechtbauer, W., & Cheung, M.W.L. (2010). Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods*, *1*, 112–125.

Voigt, R., Llorente, A.M., Jensen, C.L., Fraley, J.K., Berretta, M.C., & Heird, W.C. (2001). A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *Journal of Pediatrics*, *139*, 189–196.

Weber, W., Vander Stoep, A., McCarty, R.L., Weiss, N.S., Biederman, J., & McClellan, J. (2011). Hypericumperforatum (St John's wort) for attention-deficit/hyperactivity disorder in children and adolescents: A randomized controlled trial. *JAMA*, *299*, 2633–2641.

Wehmeier, P.M., Schacht, A., Ulberstad, F., Lehmann, M., Schneider-Fresenius, C., Lehmkuhl, G., … & Banaschewski, T. (2012). Does atomoxetine improve executive function, inhibitory control, and hyperactivity? Results from a placebo-controlled trial using quantitative measurement technology. *Journal of Clinical Psychopharmacology*, *32*, 653–660.

Weiss, R.E., Stein, M.A., & Refetoff, S. (1997). Behavioural effects of liothyronine (L-T3) in children with attention deficit hyperactivity disorder in the presence and absence of resistance to thyroid hormone. *Thyroid*, *7*, 389–393.

Williams, J.I., Cram, D.M., Tausig, F.T., & Webster, E. (1978). Relative effects of drugs and diet on hyperactive behaviors - experimental-study. *Pediatrics*, *61*, 811–817.

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